

IN THE CLAIMS:

Please substitute currently amended claim numbers 84, 86, 87, 89, 94-102, 104, 109-110 and 126 for the pending claims having the same claim numbers.

Please cancel claim numbers 85 and 90 without prejudice or disclaimer.

Claims 1-83 (canceled)

84. (currently amended) ~~A~~ An isolated variant allele nucleic acid of a human mu-opioid receptor gene, wherein said nucleic acid comprises comprising a the DNA sequence having a variation in of SEQ ID NO:1, wherein said variation comprises T67C; T124A; C153T; G174A or 187INS:GGC, or combinations thereof, except that one or more of the following variations are present:

- a) the "T" at position 279 of SEQ ID NO: 1 is replaced with a "C";
- b) the "T" at position 336 of SEQ ID NO: 1 is replaced with an "A";.
- c) the "C" at position 365 of SEQ ID NO: 1 is replaced with a "T";
- d) the "G" at position 386 of SEQ ID NO: 1 is replaced with an "A";
- e) the nucleotides "GGC" are inserted following position 401 of SEQ ID NO: 1.

85. (canceled)

86. (currently amended) The isolated ~~variant allele~~ nucleic acid of Claim ~~85~~ 84, detectably labeled.

87. (currently amended) An isolated nucleic acid molecule selectively hybridizable to the isolated ~~variant allele~~ nucleic acid of Claim ~~85~~ 84, wherein the nucleic acid has at least two variations in SEQ ID NO:1 and wherein the at least two variations are selected from:

- a) the "T" at position 279 of SEQ ID NO: 1 is replaced with a "C";
- b) the "T" at position 336 of SEQ ID NO: 1 is replaced with an "A";.

c) the “C” at position 365 of SEQ ID NO: 1 is replaced with a “T”;
d) the “G” at position 386 of SEQ ID NO: 1 is replaced with an “A”; and
e) the nucleotides “GGC” are inserted following position 401 of SEQ ID NO: 1, and
wherein said isolated nucleic acid selectively hybridizes to one or more of the variations or the
complement thereof.

88. (original) The isolated nucleic acid molecule of Claim 87, detectably labeled.

89. (currently amended) ~~A~~ An ~~variant allele of~~ isolated nucleic acid encoding a human mu opioid receptor ~~gene variant which encodes a variant human mu opioid receptor~~, wherein said variant comprises ~~comprising~~ an amino acid sequence ~~having a variation in SEQ ID NO:2,~~ wherein said ~~variation comprises Ser23Pro, Ser42Thr or the addition of a Gly residue following Gly 63~~ having one or more of the following variations in SEQ ID NO: 2:

- a) the serine at position 23 of SEQ ID NO: 2 is replaced with a proline;
- b) the serine at position 42 of SEQ ID NO: 2 is replaced with a threonine;
- c) the addition of a glycine residue following the glycine at position 63.

90. (canceled)

91. (withdrawn) A isolated variant human mu opioid receptor comprising an amino acid sequence having a variation in SEQ ID NO:2, wherein said variation comprises Ser23Pro, Ser42Thr or the addition of a Gly residue following Gly 63.

92. (withdrawn) An antibody having a variant human mu opioid receptor of Claim 91 as an immunogen.

93. (withdrawn) The antibody of Claim 92, detectably labeled

94. (currently amended) A cloning or expression vector comprising an isolated ~~variant allele~~ nucleic acid encoding ~~of~~ a human mu opioid receptor ~~gene~~ variant and an origin of replication, wherein said ~~variant allele~~ nucleic acid comprises a the DNA of claim 84.

95. (currently amended) A cloning or expression vector comprising an origin of replication and an isolated nucleic acid molecule selectively hybridizable to an isolated ~~variant allele~~ nucleic acid encoding of a human mu opioid receptor gene variant, wherein said ~~variant allele~~ nucleic acid comprises a the DNA sequence of claim 84.

96. (currently amended) An expression vector comprising an isolated ~~variant allele~~ nucleic acid encoding of a human mu opioid receptor gene variant comprising a the DNA sequence of claim 84.

97. (currently amended) An expression vector comprising an isolated nucleic acid molecule selectively hybridizable to an isolated ~~variant allele~~ nucleic acid encoding of a human mu opioid receptor gene variant, wherein said isolated nucleic acid molecule is operatively associated with a promoter, and said ~~variant allele~~ nucleic acid comprises a the DNA sequence of claim 84.

98. (currently amended) A unicellular host transformed or transfected with an expression vector comprising an isolated ~~variant allele~~ nucleic acid encoding of a human mu opioid receptor gene variant operatively associated with a promoter, wherein said ~~variant allele~~ nucleic acid comprises a the DNA sequence of claim 84.

99. (currently amended) A unicellular host transformed with an expression vector comprising an isolated nucleic acid molecule selectively hybridizable to an isolated ~~variant allele~~ nucleic acid encoding of a human mu opioid receptor gene variant, wherein said isolated nucleic acid molecule is operatively associated with a promoter, and said ~~variant allele~~ nucleic acid encoding a human mu opioid receptor variant comprises a the DNA sequence of claim 84.

100. (currently amended) An isolated ~~variant allele~~ nucleic acid encoding of a human mu opioid receptor gene variant, wherein said ~~variant allele~~ nucleic acid comprises a the DNA sequence of claim 84 having at least two variations in SEQ ID NO:1, ~~wherein said variations comprise T67C; T124A; C153T; G174A or 187INS:GGC~~ wherein at least two of the following variations are present:

- a) the “T” at position 279 of SEQ ID NO: 1 is replaced with a “C”;
- b) the “T” at position 336 of SEQ ID NO: 1 is replaced with an “A”;
- c) the “C” at position 365 of SEQ ID NO: 1 is replaced with a “T”;
- d) the “G” at position 386 of SEQ ID NO: 1 is replaced with an “A”;
- e) the nucleotides “GGC” are inserted following position 401 of SEQ ID NO: 1.

101. (currently amended) The isolated ~~variant allele~~ nucleic acid of Claim 100 detectably labeled.

102. (currently amended) An isolated nucleic acid molecule selectively hybridizable to an isolated ~~variant allele~~ nucleic acid encoding ~~of~~ a human mu opioid receptor ~~gene~~ variant comprising a the DNA sequence of claim 84, except that the variant has at least two variations in SEQ ID NO:1 and wherein the at least two variations are selected from:

- a) the “T” at position 279 of SEQ ID NO: 1 is replaced with a “C”;
- b) the “T” at position 336 of SEQ ID NO: 1 is replaced with an “A”;
- c) the “C” at position 365 of SEQ ID NO: 1 is replaced with a “T”;
- d) the “G” at position 386 of SEQ ID NO: 1 is replaced with an “A”; and
- e) the nucleotides “GGC” are inserted following position 401 of SEQ ID NO: 1, and
wherein said isolated nucleic acid selectively hybridizes to one or more of the variations or the complement thereof.

103. (original) The isolated nucleic acid molecule of Claim 102, detectably labeled.

104. (currently amended) An isolated ~~variant allele of a human mu opioid receptor gene,~~ nucleic acid, which encodes a variant human mu opioid receptor comprising an amino acid sequence having at least two variations in SEQ ID NO:2, wherein at least one said variation comprises ~~Ser23Pro, Ser42Thr or the addition of a Gly residue following Gly63~~ one of the following:

- a) the serine at position 23 of SEQ ID NO: 2 is replaced with a proline;
- b) the serine at position 42 of SEQ ID NO: 2 is replaced with a threonine;
- c) the addition of a glycine residue following the glycine at position 63.

105. (withdrawn) An isolated nucleic acid molecule selectively hybridizable to an isolated variant allele of a human mu opioid receptor gene of claim 84, wherein said variant allele comprises a DNA sequence having at least two variations in SEQ ID NO:1, and at least one of said variations comprises T67C; T124A; C153T; G174A or 187INS:GGC, so that said isolated nucleic acid molecule encodes a variant human mu opioid receptor comprising at least two variations in sequence of SEQ ID NO:2, wherein at least one of said variations comprises Ser23Pro, Ser42Thr or the addition of a Gly residue following Gly63.

106. (withdrawn) A variant human mu opioid receptor of claim 91 comprising an amino acid sequence having at least two variations in SEQ ID NO:2, wherein at least one of said variations comprises Ser23Pro, Ser42Thr or the addition of a Gly residue following Gly63.

107. (withdrawn) An antibody having a variant human mu opioid receptor of Claim 106 as an immunogen.

108. (withdrawn) The antibody of Claim 107, detectably labeled.

109. (currently amended) A cloning or expression vector comprising an isolated ~~variant allele~~ nucleic acid encoding of a human mu opioid receptor ~~gene~~ variant and an origin of replication, wherein said ~~variant allele~~ nucleic acid comprises a DNA sequence of claim 84 having at least two variations in SEQ ID NO:1, ~~wherein at least one of said variations comprises T67C; T124A; C153T; G174A; or 187INS:GGC~~ wherein at least one of the at least two variations are as follows:

- a) the "T" at position 279 of SEQ ID NO: 1 is replaced with a "C";
- b) the "T" at position 336 of SEQ ID NO: 1 is replaced with an "A";
- c) the "C" at position 365 of SEQ ID NO: 1 is replaced with a "T";
- d) the "G" at position 386 of SEQ ID NO: 1 is replaced with an "A";
- e) the nucleotides "GGC" are inserted following position 401 of SEQ ID NO:.

110. (currently amended) A cloning or expression vector comprising an origin of replication and an isolated nucleic acid molecule selectively hybridizable to an isolated ~~variant allele~~ nucleic

acid of a human mu opioid receptor gene variant, wherein said variant allele nucleic acid comprises a DNA sequence of claim 84 having at least two variations in SEQ ID NO:1, wherein at least one of said variations comprises T67C; T124A; C153T; G174A; or 187INS:GGC wherein at least one of the at least two variations are as follows:

- a) the "T" at position 279 of SEQ ID NO: 1 is replaced with a "C";
- b) the "T" at position 336 of SEQ ID NO: 1 is replaced with an "A";
- c) the "C" at position 365 of SEQ ID NO: 1 is replaced with a "T";
- d) the "G" at position 386 of SEQ ID NO: 1 is replaced with an "A";
- e) the nucleotides "GGC" are inserted following position 401 of SEQ ID NO:.

111. (original) A unicellular host transformed with an expression vector of Claim 109.

112. (original) A unicellular host transformed with an expression vector of Claim 110.

113. (withdrawn) A method for determining a susceptibility in a subject to at least one addictive disease, comprising the steps of:

- a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human mu opioid receptor gene;
- b) determining whether said human mu opioid receptor gene of said first allele comprises a DNA sequence of claim 84,

such that the presence of said at least one variation in said human mu opioid receptor gene of said first allele is expected to be indicative of the subject's susceptibility to at least one addictive disease relative to the susceptibility to said at least one addictive disease in a standard.

114. (withdrawn) The method for determining a susceptibility to at least one addictive disease of Claim 113, further comprising the step of determining whether said human mu opioid receptor gene of said second allele comprises a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises T67C; T124A; or 187INS:GGC, such that the presence of said at least one variation in said human mu opioid receptor gene of said second allele is expected to be indicative of the subject's susceptibility to said at least one addictive disease relative to the susceptibility to said at least one addictive disease in said standard.

115. (withdrawn) The method of either of Claim 114 wherein said at least one addictive disease comprises opioid addiction; cocaine addiction or addiction to other psychostimulants; nicotine addiction; barbituate or sedative hypnotic addiction; anxiolytic addiction; or alcohol addiction.

116. (withdrawn) A method for determining a susceptibility to at least one addictive disease in a subject relative to susceptibility in a standard, comprising the steps of:

- a) removing a bodily sample from said subject, wherein said sample comprises a human mu opioid receptor;
- b) determining whether said human mu opioid receptor comprises an amino acid sequence of claim 91,

such that the presence of said at least one variation is expected to be indicative of the susceptibility to said at least one addictive disease in said subject relative to susceptibility to said at least one addictive disease in said standard, wherein the human mu opioid receptor of said standard comprises an amino acid sequence of SEQ ID NO:2.

117. (withdrawn) The method of Claim 116, wherein said at least one addictive disease comprises opioid addiction; cocaine addiction or addiction to other psychostimulants; nicotine addiction; barbituate or sedative hypnotic addiction; anxiolytic addiction; or alcohol addiction.

118. (withdrawn) A method for determining a susceptibility to pain in a subject relative to a susceptibility of pain in a standard, wherein the method comprises the steps of:

- a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human mu opioid receptor gene;
- b) determining whether said human mu opioid receptor gene of said first allele comprises a DNA sequence of claim 84,

such that the presence of said at least one variation in said human mu opioid receptor gene of said first allele is expected to be indicative of susceptibility to pain in said subject relative to susceptibility to pain in said standard, wherein said first allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1.

119. (withdrawn) The method of Claim 118 for determining a susceptibility to pain in a subject, further comprising the step of determining whether said second allele of said bodily sample comprises a human mu opioid receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises T67C, T124A or 187INS:GGC, such that the presence of said at least one variation in said second allele is expected to be indicative of susceptibility to pain in said subject relative to susceptibility of pain in said standard, wherein said second allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1.

120. (withdrawn) A method for determining a therapeutically effective amount of pain reliever to administer to a subject in order to induce analgesia in said subject relative to a therapeutically effective amount of pain reliever to administer to a standard in order to induce analgesia in said standard, wherein the method comprises determining a susceptibility to pain in said subject relative to susceptibility to pain in said standard, wherein susceptibility to pain in said subject is expected to be indicative of said therapeutically effective amount of pain reliever to administer to said subject to induce analgesia in said subject relative to said therapeutically effective amount of pain reliever to administer to said standard to induce analgesia in said standard.

121. (withdrawn) The method of Claim 120 for determining a therapeutically effective amount of pain reliever to administer to said subject, wherein determining susceptibility to pain in said subject comprises the steps of:

- a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human mu opioid receptor gene; and
- b) determining whether said first allele comprises a human mu opioid receptor gene comprising a DNA sequence having a variation in SEQ ID NO:1, wherein said variation comprises T67C; T124A; C153T; G174A or 187INS:GGC, or combinations thereof,

wherein the presence of said at least one variation in said human mu opioid receptor gene of said first allele is expected to be indicative of the subject's susceptibility to pain relative to said to susceptibility of pain in said standard, wherein said first allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1, such that said

therapeutically effective amount of pain reliever to administer to the subject in order to induce analgesia is related to said susceptibility to pain in said subject relative to susceptibility to pain in said standard.

122. (withdrawn) The method of Claim 121, wherein determining susceptibility to pain in said subject relative to susceptibility to pain in said standard further comprises the step of determining whether said second allele of said bodily sample from said subject comprises a human mu opioid receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said at least one variation comprises T67C, T124A or 187INS:GGC, such that the presence of said at least one variation in said second allele is expected to be indicative of susceptibility to pain in said subject relative to susceptibility to pain in said standard, wherein said second allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1, and the therapeutically effective amount of pain reliever to administer to said subject to induce analgesia in said subject is related to the presence of said at least one variation in said human mu opioid receptor gene of said second allele of said bodily sample from said subject.

123. (withdrawn) A method for determining a therapeutically effective amount of therapeutic agent to administer to a subject suffering from at least one addictive disease to treat the at least one addictive disease in said subject relative to a therapeutically effective amount of therapeutic agent to administer to a standard suffering from the at least one addictive disease to treat the at least one addictive disease in said standard, wherein the method comprises the steps of:

- a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human mu opioid receptor gene; and
- b) determining whether said first allele comprises a human mu opioid receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises T67C, T124A or 187INS:GGC,

wherein the presence of said at least one variation in said human mu opioid receptor gene of said first allele is expected to be indicative of the therapeutically effective amount of said therapeutic agent to administer to the subject to treat said at least one addictive disease in said subject relative to said therapeutically effective amount of said therapeutic agent to administer to said

standard to treat said at least one addictive disease in said standard, wherein said first allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1.

124. (withdrawn) The method of Claim 123 for determining a therapeutically effective amount of therapeutic agent to administer to a subject suffering from said at least one addictive disease to treat said at least one addictive disease, relative to said therapeutically effective amount of said therapeutic agent administered to said standard suffering from said at least one addictive disease to treat said at least one addictive disease in said standard, further comprising the step of determining whether said second allele of said bodily sample from said subject comprises a human mu opioid receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises T67C; T124A; or 187INS:GGC, such that the presence of said at least one variation in said second allele related to said therapeutically effective amount of said therapeutic agent administered to said subject to treat said at least one addictive disease in said subject relative to said therapeutically effective amount of said therapeutic agent to administer to said standard to treat said at least one addictive disease in said standard, wherein said second allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1.

125. (withdrawn) The method of either of Claims 123 or 124, wherein said at least one addictive disease comprises opioid addiction; cocaine addiction or addiction to other psychostimulants; nicotine addiction; barbiturate or sedative hypnotic addiction; anxiolytic addiction; or alcohol addiction.

126. (currently amended) A commercial test kit ~~may~~ for determining the presence of at least one variation in a human mu opioid receptor gene ~~of an allele~~ in a bodily sample taken from a subject, wherein the commercial test kit comprises:

- a) PCR oligonucleotide primers ~~suitable for detection of an allele~~ capable of selectively hybridizing with a nucleic acid encoding ~~comprising~~ a human mu opioid receptor gene variant comprising a the DNA sequence having at least one variation in of SEQ ID NO:1

comprising T67C; T124A; C153T; G174A; or 187INS:GGC except that one or more of the following variations are present:

- i) the “T” at position 279 of SEQ ID NO: 1 is replaced with a “C”;
- ii) the “T” at position 336 of SEQ ID NO: 1 is replaced with an “A”;
- iii) the “C” at position 365 of SEQ ID NO: 1 is replaced with a “T”;
- iv) the “G” at position 386 of SEQ ID NO: 1 is replaced with an “A”;
- v) the nucleotides “GGC” are inserted following position 401 of SEQ ID NO: 1;
- b) other reagents; and
- c) directions for use of the kit.

127. (withdrawn) A commercial test kit for detecting a variant human mu opioid receptor in a bodily sample taken from a subject, comprising

- (a) predetermined amount of at least one detectably labeled immunochemically reactive component having affinity for a variant human mu opioid receptor; said variant being at least one of Ser23Pro, Ser42Thr or the addition of a Gly residue following Gly 63;
- (b) other reagents; and
- (c) directions for use of the kit.

128. (withdrawn) A commercial test kit for detecting a variant human mu opioid receptor in a bodily sample taken from a subject, wherein said kit comprises:

- (a) a labeled component which has been obtained by coupling the human mu opioid receptor of the bodily sample to a detectable label;
- (b) one or more additional immunochemical reagents of which at least one reagent is a ligand or an immobilized ligand, which ligand comprises:
 - (i) a ligand capable of binding with the labeled component (a);
 - (ii) a ligand capable of binding with a binding partner of the labeled component (a);
 - (iii) a ligand capable of binding with at least one of the component(s) to be determined; or

- (iv) a ligand capable of binding with at least one of the binding partners of at least one of the component(s) to be determined;
- (c) directions for the performance of a protocol for the detection and/or determination of one or more components of an immunochemical reaction between the human mu opioid receptor and a specific binding partner thereto.

129. (withdrawn) A method for diagnosing a disease or disorder related to a physiological function regulated by the hypothalamus pituitary adrenal axis (HPA) or the hypothalamus pituitary gonadal axis (HPG), wherein the method comprises the steps of:

- a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human mu opioid receptor gene;
- b) determining whether said human mu opioid receptor gene of said first allele comprises a DNA sequence having at least one variation in SEQ ID NO:1,

wherein said variation comprises T67C; T124A; or 187INS:GGC, such that the presence of said at least one variation in said human mu opioid receptor gene of said first allele is expected to be indicative of a disease or disorder related to a physiological function regulated by the hypothalamus pituitary adrenal axis (HPA) or the hypothalamus pituitary gonadal axis (HPG), wherein said first allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1.

130. (withdrawn) The method of Claim 129, wherein said physiological function comprises sexual or reproductive function, gastrointestinal motility, immune response, or ability to withstand stress.

131. (withdrawn) The method of Claim 130, wherein said disease or disorder comprises infertility, constipation, diarrhea, decreased immune response relative to said standard, or decreased ability to withstand stress relative to said standard.

132. (withdrawn) The method of Claim 130 for diagnosing a disease or disorder related to a physiological function regulated by the HPA or HPG, further comprising the step of determining whether said second allele of said bodily sample comprises a human mu opioid receptor gene

comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises T67C; T124A; or 187INS:GGC, such that the presence of said at least one variation in said second allele is expected to be indicative of a disease or disorder related to a physiological function regulated by the HPA or HPG axes, wherein said second allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1.

133. (withdrawn) The method of Claim 132, wherein said physiological function comprises sexual or reproductive function, gastrointestinal motility, immune response, or ability to withstand stress.

134. (withdrawn) The method of Claim 132, wherein said disease or disorder comprises infertility, constipation, diarrhea, decreased immune response relative to said standard, or decreased ability to withstand stress relative to said standard.

135. (withdrawn) The method of Claim 132, wherein said disease or disorder comprises diarrhea.

136. (withdrawn) A method for selecting an appropriate therapeutic agent and a therapeutically effective amount of said agent to administer to said subject to treating a disease or disorder related to a physiological function regulated by the HPA or HPG axes, wherein the method comprises diagnosing said disease or disorder in said subject, wherein said disease or disorder is expected to be indicative of said appropriate therapeutic agent for treating said disease or disorder.

137. (withdrawn) The method of Claim 136, wherein said physiological function comprises reproductive or sexual function, gastrointestinal motility, immune response, or ability to withstand stress.

138. (withdrawn) The method of Claim 136, wherein diagnosing said disease or disorder in said subject comprises the steps of:

- a) removing a bodily sample from said subject, wherein said sample comprises a first and second allele comprising a human mu opioid receptor gene; and
- b) determining whether said first allele comprises a human mu opioid receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said at least one variation comprises T67C; T124A; or 187INS:GGC,

wherein the presence of said at least one variation in said human mu opioid receptor gene of said first allele is expected to be indicative of said disease or disorder related to a physiological function regulated by the HPA or HPG axes.

139. (withdrawn) The method of Claim 138, wherein diagnosing a disease or disorder related to a physiological function regulated by the HPA or HPG further comprises the step of determining whether said second allele of said bodily sample comprises a human mu opioid receptor gene comprising a DNA sequence having at least one variation in SEQ ID NO:1, wherein said variation comprises T67C; T124A; or 187INS:GGC, such that the presence of said at least one variation in said second allele is expected to be indicative of a disease or disorder related to a physiological function regulated by the HPA or HPG axes, wherein said second allele of said standard comprises a human mu opioid receptor gene comprising a DNA sequence of SEQ ID NO:1.

140. (withdrawn) The method of Claim 139, wherein said physiological function comprises reproductive or sexual function, gastrointestinal motility, immune response, or ability to withstand stress.

141. (withdrawn) The method of Claim 139, wherein said disease or disorder comprises infertility, constipation, diarrhea, decreased immune response relative to immune response in said standard, or decreased ability to withstand stress relative to ability to withstand stress of said standard.